Determinants of Vitamin D Status in Caucasian Adults: Influence of Sun Exposure, Dietary Intake, Sociodemographic, Lifestyle, Anthropometric, and Genetic Factors

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Very few studies have investigated the determinants of serum vitamin D levels using a set of variables that include simultaneously sun exposure, phototype, dietary intake, sociodemographics, anthropometric, lifestyle data, and genetic polymorphisms. Our objective was to investigate the associations between all these parameters and vitamin D status in a large sample of French adults. This cross-sectional survey was based on 1,828 middle-aged Caucasian adults from the SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) study. Plasma 25-hydroxyvitamin D (25OHD) concentration was lower among women ($P<0.0001$), older subjects ($P=0.04$), obese/underweight ($P<0.0001$), those living at higher latitudes ($P<0.0001$), those whose blood draw occurred in early spring ($P<0.0001$), less physically active ($P<0.0001$), with low sun exposure ($P<0.0001$), and with no-to-low alcohol intake ($P=0.0001$). Mutant GC rs4588 and rs7041 single nucleotide polymorphisms were associated with lower and higher 25OHD concentrations, respectively ($P<0.0001$). Dietary intake was not a major determinant of vitamin D status ($P=0.7$). This study provides an overall picture of determinants of vitamin D status. Several modifiable factors were identified, such as daily-life moderate sun exposure, physical activity, and normal-weight maintenance, which should be targeted by public health policies in order to improve vitamin D status in the general population, while avoiding active/intensive sun exposure, in line with recommendations for skin cancer prevention.

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INTRODUCTION

Vitamin D is a pro-hormone that has a critical role in the phosphocalcic metabolism, and sufficient vitamin D levels are essential for optimal bone mineral density. Vitamin D can be supplied from dietary sources but is mainly generated endogenously from skin exposure to sunlight via the epidermis, which is the main site of vitamin D3 photosynthesis (Lehmann *et al.*, 2004; Reichrath, 2007). In addition, the vitamin D receptor (VDR) located within the keratinocytes makes these cells a unique photoendocrine vitamin D system that is stimulated by UVB irradiation (Holick, 2007). Binding of vitamin D on keratinocyte VDR enhances the production of cathelicidins, which have potent microbicidal activities and are a major component of the innate immune system (Zasloff, 2005). This argues for an important role of vitamin D in immune defense. Indeed, most tissues and cells in the body express VDRs, and several tissues possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D (25OHD), to the active form, 1,25-dihydroxyvitamin D. Besides its immune-modulatory and anti-inflammatory properties, there is now increasing epidemiological and experimental evidence for a protective effect of vitamin D not only on the risk of fall and fracture but also on dental health, colorectal cancer, hypertension, and cardio-

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Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; SU.VI.MAX, SUpplémentation en VItamines et Minéraux AntioXydants

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vascular mortality (Rosen, 2011; Touvier *et al.*, 2011; Vimaleswaran *et al.*, 2014). Thus, reaching and maintaining an optimal vitamin D status at all life stages is of major individual and public health importance.

Some determinants of vitamin D status are now well established. This is the case, for instance, for sun exposure (Holick, 2007) and physical activity (Freedman *et al.*, 2013), both known to be associated with increased vitamin D status. However, even for these later factors, some issues remain. Indeed, the optimal level of usual sun exposure needed to positively impact vitamin D status is still undetermined. This question is crucial considering that excessive sun exposure is the most established risk factor for skin cancer and premature skin aging (Glossmann, 2013; Petersen *et al.*, 2014). Regarding physical activity, it is still unclear whether this factor has a causal influence on vitamin D status as such, or whether the influence is only from sun exposure during outdoor physical activity practices. Besides, other potential lifestyle correlates of vitamin D status, such as alcohol intake, have been poorly investigated (Bertrand *et al.*, 2012; Engelman *et al.*, 2013; Saquib *et al.*, 2006; Shirazi *et al.*, 2013; Thuesen *et al.*, 2012).

Single nucleotide polymorphisms (SNPs) of genes involved in vitamin D and/or calcium metabolism could also influence circulating 25OHD concentrations (Hiraki *et al.*, 2013; Wang *et al.*, 2010). Of particular interest are genes coding for the *VDR*, the vitamin D-deactivating enzyme 24-α hydroxylase (*CYP24A1*), the calcium-sensing receptor (*CASR*), the retinoid X receptor (*RXR*, which forms a heterodimer with the VDR upon vitamin D activation), and the *GC* gene (encoding for the vitamin D-binding protein). However, little is known regarding the associations of these genes with vitamin D status (Trummer *et al.*, 2012; Bouillon, 2010; Engelman *et al.*, 2008, 2013; Ahn *et al.*, 2010).

Finally, to our knowledge, only one study has assessed the co-influence of sun exposure, phototype, dietary vitamin D intake, physical activity, anthropometry, sociodemographic and lifestyle factors, and genetic polymorphisms on vitamin D status, simultaneously in the same population, and it was restricted to at-risk subjects—i.e., post-menopausal women (Engelman *et al.*, 2013). Thus, our objective was to investigate the relative association of all these parameters with vitamin D status in a large sample of French middle-aged Caucasian adults.

RESULTS

Characteristics of the study population are described in Table 1. Participants were Caucasian middle-aged men and women. Mean 25OHD plasma concentration was 20.0 ng ml^{-1} (SD = 10.3); 14.8% of subjects had a vitamin D status ⩽10 ng ml^{-1} and 57.8% had a vitamin D status ⩽20 ng ml^{-1}. Mean plasma parathyroid hormone (PTH) concentration was 26.3 ng l^{-1} (SD = 9.4).

All studied SNPs respected the Hardy–Weinberg equilibrium ($P>0.05$), except *VDR* BsmI rs1544410 and *VDR* FokI rs2228570/10735810 (both $P=0.01$). The repartition of subjects across the different genotypes was in accordance with that observed in European reference populations (CSHL-HapMap-CEU and 1000GENOMES-phase_1_EUR) for all SNPs ($P>0.05$).

Vitamin D status was lower among women ($P<0.0001$), older subjects ($P=0.04$), obese or underweight subjects ($P<0.0001$), subjects who lived at higher latitudes ($P<0.0001$), and those whose blood draw occurred in early spring ($P<0.0001$; Supplementary Table 1 online). Conversely, vitamin D status was higher among subjects who were more physically active ($P<0.0001$), who had higher scores of usual sun exposure ($P<0.0001$), those with higher Fitzpatrick phototype (among Caucasians, $P=0.03$), and those who drank more alcohol ($P=0.0001$; Supplementary Table 1 online).

Among the 10 studied SNPs, mutant *GC* rs4588 was associated with lower vitamin D status, whereas mutant *GC rs7041* was associated with higher vitamin D status (both $P<0.0001$; Supplementary Table 2 online).

Consistently, risk of 25OHD deficiency was higher among women ($OR_{women\ vs.\ men}=2.6$, 95% confidence interval (CI) = (1.6–4.3), $P<0.0001$), obese and underweight subjects ($OR_{obese\ vs.\ normal}=3.9$ (2.2–7.0), $OR_{underweight\ vs.\ normal}=3.1$ (1.1–9.2), $P<0.0001$), subjects who lived at higher latitudes ($OR_{Q4\ vs.\ Q1}=3.2$ (2.0–5.0), $P<0.0001$), and those whose blood draw occurred in early spring ($OR_{April–May\ vs.\ October–November}=3.7$ (1.9–7.0), $P<0.0001$; Table 2). Risk of 25OHD deficiency was lower among subjects who were more physically active ($OR_{\geqslant 1\,h\ per\ day\ vs.\ irregular}=0.4$ (0.3–0.7), $P<0.0001$), who had higher scores of usual sun exposure ($OR_{Q4\ vs.Q1}=0.2$ (0.1–0.3), $P<0.0001$), those with higher Fitzpatrick phototype (among Caucasians, $OR_{IV\ vs.\ I}=0.4$ (0.2–0.99), $P=0.04$), and those who drank more alcohol ($OR_{Q4\ vs.Q1}=0.5$ (0.3–0.8), $P=0.006$; Table 2).

Mutant *GC* rs4588 was associated with higher risk of 25OHD deficiency ($OR_{MT\ vs.\ WT}=4.9$ (3.0–8.1), $P<0.0001$), whereas mutant *GC* rs7041 was associated with lower risk ($OR_{MT\ vs.\ WT}=0.3$ (0.2–0.5), $P<0.0001$; Table 3).

Associations were very similar regarding the risk of 25OHD insufficiency (Tables 2 and 3).

Dietary intake of vitamin D, smoking status, and educational level were not related to vitamin D status in any model (Supplementary Tables 1 and 2 online), nor were menopausal status and hormonal treatment for menopause (data not shown).

In multivariate models, higher practice of mountain sports ($OR_{Q4\ vs.\ Q1}=0.4$ (0.2–0.8), $P=0.003$) and outdoor hobbies ($OR_{Q4\ vs.\ Q1}=0.6$ (0.4–0.9), $P=0.01$) was independently associated with lower risk of 25OHD deficiency. No association was observed for nautical sports ($P=0.9$). The adjunction of these outdoor sports or hobbies into the multivariate model did not modify the findings for all other covariates (including physical activity).

All associations between 25OHD concentrations, risk of vitamin D deficiency, risk of vitamin D insufficiency, and nongenetic parameters were maintained when genetic factors were entered in the models (data not shown). Further adjustment for energy intake did not modify the findings. When a stepwise selection of covariates was performed, all main

Table 1. Characteristics of the study population ($N = 1,828$)

	25OHD ⩽ 10 ng ml^{-1}, $N = 271$		10 < 25OHD ⩽ 20 ng ml^{-1}, $N = 785$		25OHD > 20 ng ml^{-1}, $N = 772$	
	N (%)	Mean ± SD	*N* (%)	Mean ± SD	*N* (%)	Mean ± SD
Gender						
Men	94 (34.7)		327 (41.7)		412 (53.4)	
Women	177 (65.3)		458 (58.3)		360 (46.6)	
Age (years)						
<40	12 (4.4)		42 (5.4)		48 (6.2)	
40–44	34 (12.5)		88 (11.2)		65 (8.4)	
45–49	72 (26.6)		219 (27.9)		190 (24.6)	
50–54	68 (25.1)		205 (26.1)		192 (24.9)	
55–65	85 (31.4)		231 (29.4)		277 (35.9)	
Alcohol intake (g per d)		14.1 ± 17.5		18.3 ± 20.4		21.7 ± 21.9
Quartile 1		1.7 ± 2.9		1.9 ± 3.0		2.7 ± 3.6
Quartile 2		7.8 ± 7.2		9.1 ± 7.4		11.3 ± 7.6
Quartile 3		16.9 ± 11.8		20.4 ± 12.0		21.4 ± 12.3
Quartile 4		38.9 ± 19.7		42.0 ± 23.2		47.3 ± 23.0
Body mass index (kg m^{-2})						
<18.5	8 (2.9)		21 (2.7)		8 (1.0)	
⩾18.5–<25	150 (55.4)		449 (57.2)		504 (65.3)	
⩾25–<30	76 (28.0)		263 (33.5)		231 (29.9)	
⩾30	37 (13.7)		52 (6.6)		29 (3.8)	
Physical activity						
Irregular	83 (30.6)		212 (27.0)		139 (18.0)	
<1 h per d walking equivalent	97 (35.8)		247 (31.5)		210 (27.2)	
⩾1 h per d walking equivalent	91 (33.6)		326 (41.5)		423 (54.8)	
Smoking status						
Never smoker	145 (53.5)		416 (53.0)		351 (45.5)	
Former smoker	96 (35.4)		269 (34.3)		330 (42.7)	
Current smoker	30 (11.1)		100 (12.7)		91 (11.8)	
Educational level						
Primary	68 (25.1)		181 (23.1)		162 (21.0)	
Secondary	109 (40.2)		270 (34.4)		311 (40.3)	
Superior	94 (34.7)		334 (42.5)		299 (38.7)	
Menopausal status						
Nonmenopausal	108 (61.0)		280 (61.1)		213 (59.2)	
Menopausal	69 (39.0)		178 (38.9)		147 (40.8)	
Hormonal treatment for menopause						
Yes	61 (34.5)		156 (34.1)		144 (40.0)	
Dietary intake of vitamin D (μg per d)		2.7 ± 1.8		2.8 ± 1.9		2.9 ± 2.0
Latitude		47.5 ± 1.8		47.2 ± 3.1		46.5 ± 2.1
Month of blood draw						
October–November	21 (7.8)		108 (13.8)		176 (22.8)	
December–January	72 (26.6)		225 (28.7)		290 (37.5)	
February–March	134 (49.4)		359 (45.7)		239 (31.0)	
April–May	44 (16.2)		93 (11.8)		67 (8.7)	
Score for intensity of lifetime sun exposure		3.2 ± 3.4		4.3 ± 3.4		5.2 ± 3.4
Fitzpatrick phototype[1]						
I	20 (7.4)		34 (4.3)		19 (2.5)	
II	76 (28.0)		206 (26.3)		146 (18.9)	
III	141 (52.0)		425 (54.1)		454 (58.8)	
IV	34 (12.6)		120 (15.3)		153 (19.8)	
VDR *BsmI rs1544410*[2]						
C/C (WT)	86 (35.0)		271 (36.7)		259 (36.6)	

Table 1. (Continued)

	25OHD ⩽ 10 ng ml^{-1}, N = 271		10 < 25OHD ⩽ 20 ng ml^{-1}, N = 785		25OHD > 20 ng ml^{-1}, N = 772	
	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD
C/T (HT)	111 (45.1)		332 (45.0)		321 (45.3)	
T/T (MT)	49 (19.9)		135 (18.3)		128 (18.1)	
VDR *FokI rs2228570/10735810*[2]						
G/G (WT)	106 (39.6)		315 (40.8)		319 (42.1)	
A/G (HT)	123 (45.9)		335 (43.3)		329 (43.5)	
A/A (MT)	39 (14.5)		123 (15.9)		109 (14.4)	
VDR *Cdx2 rs11568820*[2]						
C/C (WT)	147 (56.1)		434 (57.9)		430 (58.2)	
C/T (HT)	98 (37.4)		269 (35.9)		269 (36.4)	
T/T (MT)	17 (6.5)		47 (6.2)		40 (5.4)	
CYP24A1 *rs48099583*[2]						
T/T (WT)	179 (67.8)		544 (72.2)		497 (68.0)	
G/T (HT)	77 (29.2)		194 (25.8)		220 (30.1)	
G/G (MT)	8 (3.0)		15 (2.0)		14 (1.9)	
GC *rs4588*[2]						
G/G (WT)	99 (37.6)		356 (47.0)		418 (55.5)	
G/T (HT)	116 (44.1)		331 (43.7)		284 (37.7)	
T/T (MT)	48 (18.3)		71 (9.4)		51 (6.8)	
GC *rs7041*[2]						
A/A (WT)	73 (27.5)		167 (21.8)		130 (17.3)	
A/C (HT)	132 (49.6)		372 (48.6)		339 (45.1)	
C/C (MT)	61 (22.9)		227 (29.6)		283 (37.6)	
RXR *rs7861779*[2]						
C/C (WT)	183 (73.8)		562 (76.1)		556 (77.7)	
C/T (HT)	60 (24.2)		167 (22.6)		149 (20.7)	
T/T (MT)	5 (2.0)		10 (1.3)		11 (0.6)	
RXR *rs12004589*[2]						
G/G (WT)	200 (76.9)		582 (77.0)		593 (79.9)	
G/T (HT)	55 (21.2)		169 (22.3)		139 (18.7)	
T/T (MT)	5 (1.9)		5 (0.7)		10 (1.4)	
CASR *rs1801725*[2]						
G/G (WT)	174 (66.4)		543 (70.9)		538 (71.9)	
G/T (HT)	83 (31.7)		201 (26.2)		195 (26.1)	
T/T (MT)	5 (1.9)		22 (2.9)		15 (2.0)	
CASR *rs4678174*[2]						
T/T (WT)	126 (49.2)		356 (48.3)		368 (50.9)	
C/T (HT)	107 (41.8)		313 (42.5)		283 (39.1)	
C/C (MT)	23 (9.0)		68 (9.2)		72 (10.0)	
Plasma 25OHD concentration (ng ml^{-1})		7.6 ± 1.6		15.0 ± 2.8		29.6 ± 8.4
Plasma PTH concentration (ng l^{-1})		30.4 ± 11.7		26.4 ± 9.3		24.7 ± 7.9

Abbreviations: HT, heterozygous type; MT, homozygous mutant type; PTH, parathyroid hormone; WT, wild type; 25OHD, 25-hydroxyvitamin D.
[1]I: always burns, never tans; II: burns easily, tans minimally; III: burns moderately, tans uniformly; and IV: burns minimally, always tans well.
[2]Missing data were as follows: 136 (rs1544410), 30 (rs2228570/10735810), 77 (rs11568820), 80 (rs4809958), 54 (rs4588), 44 (rs7041), 125 (rs78617793), 70 (rs120045893), 52 (rs18017253), and 112 (rs46781743). For nongenetic covariates, <5% of values were missing and were replaced by the mode.

associations with vitamin D status were maintained in all models (for gender, alcohol intake, body mass index (BMI), physical activity, latitude, month of blood draw, intensity of sun exposure, *GC* rs4588, and *GC* rs7041), whereas weaker associations (for age and Fitzpatrick phototype) were not (data not shown).

Higher PTH concentrations were associated with older age ($P = 0.008$), higher BMI ($P = 0.007$), lower dietary vitamin D

Table 2. Associations between 25OHD status (three classes) and nongenetic factors, SU.VI.MAX cohort, France (*N* = 1,828)

	n	>10–⩽20 vs. >20 ng ml^{-1}		⩽10 vs. >20 ng ml^{-1}		*P*[1]
		OR	95% CI	OR	95% CI	
Gender						<0.0001[§]
Men	833	1.0		1.0		
Women	995	1.8	1.3–2.5	2.6	1.6–4.3	
Age (years)						0.2[§]
<40	102	1.0		1.0		
40–44	187	1.6	0.9–2.8	2.3	1.0–5.3	
45–49	481	1.7	1.1–2.9	2.3	1.1–4.9	
50–54	465	1.9	1.1–3.1	2.8	1.3–6.1	
55–65	593	1.5	0.9–2.5	2.5	1.1–5.4	
Alcohol intake[2]						0.006
Quartile 1	456	1.0		1.0		
Quartile 2	457	0.9	0.6–1.2	0.9	0.6–1.4	
Quartile 3	458	0.8	0.6–1.1	0.6	0.4–0.9	
Quartile 4	457	0.8	0.6–1.1	0.5	0.3–0.8	
Body mass index (kg m^{-2})						<0.0001[§]
<18.5	37	2.6	1.1–6.2	3.1	1.1–9.2	
⩾18.5–<25	1,103	1.0		1.0		
⩾25–<30	570	1.4	1.1–1.9	1.3	0.9–1.8	
⩾30	118	2.0	1.2–3.3	3.9	2.2–7.0	
Physical activity						<0.0001
Irregular	434	1.0		1.0		
<1 h per d walking equivalent	554	0.8	0.6–1.1	0.9	0.6–1.3	
⩾1 h per d walking equivalent	840	0. 6	0.4–0.7	0.4	0.3–0.7	
Smoking status						0.3[§]
Never smoker	912	1.0		1.0		
Former smoker	695	0.8	0.6–1.0	1.0	0.7–1.5	
Current smoker	221	1.0	0.7–1.5	1.1	0.7–1.9	
Educational level						0.3
Primary	411	1.0		1.0		
Secondary	690	0.7	0.5–1.0	0.7	0.5–1.1	
Superior	727	0.98	0.7–1.3	0.7	0.5–1.1	
Dietary intake of vitamin D[2]						0.7
Quartile 1	456	1.0		1.0		
Quartile 2	457	1.2	0.9–1.7	0.9	0.6–1.4	
Quartile 3	458	1.1	0.8–1.5	1.0	0.6–1.5	
Quartile 4	457	1.0	0.7–1.3	0.8	0.5–1.2	
Latitude[2]						<0.0001
Quartile 1	459	1.0		1.0		
Quartile 2	478	1.1	0.8–1.4	1.0	0.6–1.7	
Quartile 3	424	1.7	1.3–2.4	2.3	1.5–3.8	
Quartile 4	467	2.1	1.5–2.9	3.2	2.0–5.0	
Month of blood draw						<0.0001
October–November	305	1.0		1.0		
December–January	587	1.3	0.9–1.8	2.3	1.3–4.0	

Table 2. (Continued)

	n	>10–⩽20 vs. >20 ng ml^{-1}		⩽10 vs. >20 ng ml^{-1}		*P*[1]
		OR	95% CI	OR	95% CI	
February–March	732	2.4	1.8–3.3	4.8	2.8–8.2	
April–May	204	1.7	1.1–2.7	3.7	1.9–7.0	
Intensity of lifetime sun exposure[2]						<0.0001
Quartile 1	364	1.0		1.0		
Quartile 2	589	0.7	0.5–1.0	0.4	0.3–0.6	
Quartile 3	391	0.5	0.4–0.7	0.2	0.1–0.4	
Quartile 4	484	0.5	0.3–0.6	0.2	0.1–0.3	
Fitzpatrick phototype[3]						0.04
I	73	1.0		1.0		
II	428	0.9	0.5–1.8	0.7	0.3–1.5	
III	1020	0.8	0.4–1.5	0.7	0.3–1.5	
IV	307	0.7	0.3–1.3	0.4	0.2–1.0	

Abbreviations: CI, confidence interval; OR, odds ratio; 25OHD, 25-hydroxyvitamin D.
Three classes of 25OHD status: deficiency, ⩽10 ng ml^{-1}/insufficiency, 10<25OHD⩽20 ng ml^{-1}/reference = normal status, 25OHD>20 ng ml^{-1}.
[1]*P* non-trend (§) or *P* for linear trend from a multivariate model of unconditional polytomous logistic regression including all studied nongenetic factors and adjusted for the number of dietary records. Polytomous logistic regression models permit estimation of simultaneous odds in a single model. The three 25OHD categories were modeled as a nominal dependent variable.
[2]Cutoffs for quartiles of continuous variables were as follow: alcohol intake (g per d), 11.3/24.0/42.8 in men and 1.4/5.8/15.4 in women; vitamin D intake (μg per d), 1.7/2.7/4.1 in men and 1.4/2.1/3.3 in women; latitude (°), 45.4/48/48.5; and intensity of lifetime exposure (score, 0–10), 1.7/4.4/8.2.
[3]I: always burns, never tans; II: burns easily, tans minimally; III: burns moderately, tans uniformly; and IV: burns minimally, always tans well. Only these four phototypes were represented in this Caucasian population.

intake ($P=0.0003$), higher latitude ($P<0.0001$), and blood draw in winter/early spring ($P<0.0001$; Supplementary Table 3 online). None of the tested SNPs was associated with PTH concentrations (data not shown).

DISCUSSION

This study investigated a wide range of potential determinants of vitamin D status simultaneously in a same data set. In this large middle-aged Caucasian population, female gender, under- and overweight, low physical activity, low sun exposure, lower alcohol intake, homozygous mutant type of the *GC* rs4588, and wild type of the *GC* rs7041 SNPs were independently associated with low plasma 25OHD concentrations and thus higher risk of 25OHD deficiency.

As usually observed (Hintzpeter *et al.*, 2008; Mithal *et al.*, 2009; van der Wielen *et al.*, 1995), women were at higher risk of 25OHD deficiency and insufficiency. Also consistent with previous publications (Bertrand *et al.*, 2012; Greene-Finestone *et al.*, 2011; Daly *et al.*, 2012), overweight and obesity were associated with higher risk of vitamin D deficiency. In an intervention study on overweight/obese post-menopausal women (Mason *et al.*, 2011), weight loss was associated with an increase in serum 25OHD concentration, strengthening the plausibility of a causal association. The relationship between underweight (BMI<18.5 kg m^{-2}) and vitamin D status has been poorly documented in the literature, but our result of an inverse association is consistent with available knowledge (Hintzpeter *et al.*, 2008).

Higher latitude (associated with lower amounts of sunshine), winter/early spring season, and low sun exposure (Major *et al.*, 2013; Holick, 2007; Saquib *et al.*, 2006) have been associated with higher risk of 25OHD deficiency in the literature, consistent with our findings. Although many studies used time spent exercising or outdoors in the garden (Lucas *et al.*, 2005) or leisure-time physical activity (Giovannucci *et al.*, 2006) as surrogate markers of sunshine exposure, our study collected detailed information about usual practices of sun exposure (intensity, length, frequency, protection habits, and so on) compiled into a validated score (Guinot *et al.*, 2001; Ezzedine *et al.*, 2008, 2013; Elfakir *et al.*, 2010). Interestingly, improvement of vitamin D status was observed starting from the second quartile of the score of sun exposure and was relatively stable over the third and fourth quartiles. These results suggest that even low daily-life sun exposure behaviors contribute to increase vitamin D synthesis and improve 25OHD concentrations. Definitely, such findings are compatible with recommendations to avoid excessive and active sun exposure for the prevention of UV damage and skin cancers.

A positive linear association was observed between physical activity and plasma 25OHD concentrations in our study, consistent with previous literature (Thuesen *et al.*, 2012; Engelman *et al.*, 2013; Berger *et al.*, 2012). Interestingly, this result was adjusted for sun exposure and remained statistically significant even after adjustment for the practice of outdoor hobbies or sports (mountain or nautical). This suggests that

Table 3. Associations between 25OHD status (three classes) and 10 selected SNPs, SU.VI.MAX cohort, France (*N* = 1,828)

	n	>10–⩽20 vs. >20 ng ml^{-1}		⩽10 vs. >20 ng ml^{-1}		*P*-trend[1]
		OR	95% CI	OR	95% CI	
VDR *BsmI rs1544410*[2]						0.6
WT	616	1.0		1.0		
HT	764	1.0	0.8–1.3	1.1	0.7–1.5	
MT	312	1.0	0.7–1.4	1.2	0.8–1.9	
VDR *FokI rs2228570/10735810*[2]						0.6
WT	740	1.0		1.0		
HT	787	1.0	0.8–1.3	1.1	0.8–1.6	
MT	271	1.1	0.8–1.6	1.1	0.7–1.8	
VDR *Cdx2 rs11568820*[2]						0.9
WT	1,011	1.0		1.0		
HT	636	1.0	0.8–1.2	1.1	0.8–1.5	
MT	104	1.2	0.7–1.9	1.2	0.6–2.3	
CYP24A1 *rs4809958*[2]						0.2
WT	1,220	1.0		1.0		
HT	491	0.8	0.6–1.0	1.0	0.7–1.4	
MT	37	1.0	0.4–2.1	1.4	0.5–3.9	
GC *rs4588*[2]						<0.0001
WT	873	1.0		1.0		
HT	731	1.5	1.2–1.9	2.0	1.5–2.9	
MT	170	1.8	1.2–2.8	4.9	3.0–8.1	
GC *rs7041*[2]						<0.0001
WT	370	1.0		1.0		
HT	843	0.8	0.6–1.0	0.6	0.4–1.0	
MT	571	0.6	0.4–0.7	0.3	0.2–0.5	
RXR *rs7861779*[2]						0.8
WT	1,301	1.0		1.0		
HT	376	1.1	0.8–1.4	1.2	0.8–1.8	
MT	26	1.0	0.4–2.4	1.2	0.4–4.3	
RXR *rs12004589*[2]						0.8
WT	1,375	1.0		1.0		
HT	363	1.1	0.9–1.5	1.1	0.8–1.6	
MT	20	0.5	0.2–1.7	1.3	0.4–4.8	
CASR *rs1801725*[2]						0.3
WT	1,255	1.0		1.0		
HT	479	1.1	0.9–1.4	1.5	1.0–2.1	
MT	42	1.3	0.7–2.7	0.8	0.3–2.5	
CASR *rs4678174*[2]						0.7
WT	850	1.0		1.0		
HT	703	1.3	1.0–1.6	1.3	0.9–1.8	
MT	163	0.9	0.6–1.4	0.8	0.4–1.4	

Abbreviations: CI, confidence interval; HT, heterozygous type; MT, homozygous mutant type; OR, odds ratio; SNPs, single nucleotide polymorphisms; WT, wild type; 25OHD, 25-hydroxyvitamin D.
Three classes of 25OHD status: deficiency, ⩽10 ng ml^{-1}/insufficiency, 10<25OHD⩽20 ng ml^{-1}/reference = normal status, 25OHD>20 ng ml^{-1}.

[1]*P* for linear trend from multivariate models of unconditional polytomous logistic regression adjusted for sex, age, alcohol intake, body mass index, physical activity, smoking status, educational level, number of dietary records, vitamin D dietary intake, latitude of the living city, month of blood draw, intensity of lifetime sun exposure, and Fitzpatrick phototype. One model was computed for each SNP. Polytomous logistic regression models permit estimation of simultaneous odds in a single model. The three 25OHD categories were modeled as a nominal dependent variable.

[2]*n* for missing data were as follows: 136 (rs1544410), 30 (rs2228570/10735810), 77 (rs11568820), 80 (rs4809958), 54 (rs4588), 44 (rs7041), 125 (rs78617793), 70 (rs120045893), 52 (rs18017253), and 112 (rs46781743).

physical activity as such (and not only via sun exposure during such activities) could be causally associated with better vitamin D status, as supported by the few studies in which both exposures were measured simultaneously (Brock *et al.*, 2010; Bell *et al.*, 1988).

In our population study, alcohol intake (which was moderate) was positively correlated with vitamin D status. Although excessive alcohol intake has been associated with lower 25OHD concentrations (Bjorneboe *et al.*, 1986), the same positive association between moderate alcohol intake and better vitamin D status has been observed in several previous studies (Bertrand *et al.*, 2012; Saquib *et al.*, 2006; Shirazi *et al.*, 2013; Thuesen *et al.*, 2012; Engelman *et al.*, 2013; Larose *et al.*, 2014; McCullough *et al.*, 2010; Lee *et al.*, 2012). Whether this relationship is causal or only due to residual confounding remains unclear. However, it remained significant even after extensive adjustment for potential confounders. Consistently, several studies showed that bone mineral density was higher among moderate alcohol consumers (Orwoll *et al.*, 2000; Saquib *et al.*, 2006). The biochemical processes underlying the relationship between alcohol and vitamin D concentrations are complex. One possible hypothesis is that alcohol might be a suppressor of PTH secretion and thus responsible for a decrease in serum conversion of 25OHD to 1,25-dihydroxyvitamin D (Turner *et al.*, 1988; McCarty and Thomas, 2003). Unconverted 25OHD may be responsible for higher serum 25OHD concentrations. However, even if a causal association is confirmed by future studies, alcohol intake, even moderate, should evidently not be recommended as a lever for vitamin D status improvement, because of its adverse effects on other health outcomes such as cancers (AICR/WCRF, 2007).

Several methodological reasons, such as the potentially nonlinear association of 25OHD levels at the low range and the inaccuracies inherent in assessing dietary intake, may explain the null association between dietary vitamin D intake and 25OHD concentrations. However, mean daily dietary vitamin D intake in our study population (2.9 μg per day) was below the daily recommended intake of 5 μg per day for French adults <75 years and far below international recommendations (Institute of Medicine, 2011), some groups recommending at least 20 μg per day of dietary/supplemental vitamin D intake (Brouwer-Brolsma *et al.*, 2013). This probably largely explains why we did not observe any association between dietary vitamin D intake and 25OHD plasma concentrations, consistent with several studies in Europe (Thuesen *et al.*, 2012; Perna *et al.*, 2012; van der Wielen *et al.*, 1995). Indeed, in France, dietary sources of vitamin D are more limited than in other countries where dietary vitamin D intake is positively associated with vitamin D status (Freedman *et al.*, 2013; Snellman *et al.*, 2009; Zgaga *et al.*, 2011). As some foods fortified with vitamin D (such as vegetable oils) appeared on the French market in the last decade, it would be useful to re-conduct this study for data update. However, as previously underlined, mean daily vitamin D intake in our study was very similar to the level observed in a recent French national survey (2.6 μg per day; Dubuisson *et al.*, 2010).

Dietary supplement use was not allowed for participants of the SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) trial; thus, an impact of the use of such products on vitamin D status could not be investigated. However, a few subjects ($n=12$, excluded from the present analysis) took medication containing vitamin D. Their status was substantially higher than non-supplemented subjects (35.1 vs. 20.0 ng ml^{-1}, data not shown).

The *GC* gene contains at least six nonsynonymous SNPs, two with relatively common frequency (McCullough *et al.*, 2009; rs7041 and rs4588, with respective minor allele frequency C = 0.386/840 and T = 0.216/471 according to the 1000GENOMES database). These two SNPs were strongly and independently associated with vitamin D status in our population study. Both rs7041 and rs4588 were also associated with vitamin D status in some previous studies (Trummer *et al.*, 2012; Engelman *et al.*, 2008, 2013; Ahn *et al.*, 2010). The vitamin D-binding protein, encoded by the *GC* gene, belongs to the albumin family. It greatly facilitates vitamin D actions by carrying vitamin D metabolites to various sites of action, and polymorphic vitamin D-binding proteins differ in their affinities for 25OHD (Powe *et al.*, 2013).

Overall, results on PTH correlates were consistent with those on 25OHD. However, although dietary intake of vitamin D was poorly correlated with 25OHD status, the association seemed stronger regarding PTH (inverse association). Additional epidemiological and experimental studies are needed to further elucidate this result.

In terms of public health, the interest of our results is that several modifiable risk factors of vitamin D deficiency were identified. A substantial potential impact (+32.7%) on increasing vitamin D status was observed for normal weight compared with obese subjects. Consistently, Vimaleswaran *et al.* (2013) recently demonstrated the causality of this association by a bidirectional Mendelian randomization analysis of multiple cohorts and concluded that population level interventions to reduce BMI are expected to decrease the prevalence of vitamin D deficiency. Other potential impacts of modifiable risk factors were +15% of 25OHD concentrations for those who practiced at least 1 h per day walking equivalent compared with irregular physical activity and +16.3% for low-to-moderate daily-life sun exposure (quartile 2 of the score) compared with no sun exposure at all (quartile 1).

Some limitations should be acknowledged. First, caution is needed when extrapolating our results to the entire middle-aged Caucasian French population. Indeed, our subjects were volunteers participating in a nutritional intervention study (Hercberg *et al.*, 2004) who generally had a higher educational level and occupational status compared with the general population. However, the mean plasma 25OHD concentration observed in this study (20.0 ng ml^{-1}) was very close to the value observed in a French nationally representative survey conducted in 2006–2007 on adults aged ⩾18 years (23.2 ng ml^{-1}; Castetbon *et al.*, 2009), although slightly lower probably because of an overall older age of our study population and the use of a different kit for the 25OHD assay. Next, measurements of 25OHD concentrations were not taken by a mass spectrometry method, and there were no

data available on the vitamin D-binding protein. However, the Roche Vitamin D Total assay is judged suitable for measurement of total 25OHD in serum and Li-heparin plasma (Knudsen *et al.*, 2012). Finally, other genes such as *CYP2R1* or *NADSYN1* could also influence vitamin D status (Hiraki *et al.*, 2013; Wang *et al.*, 2010; Engelman *et al.*, 2013; Ahn *et al.*, 2010; Bu *et al.*, 2010), for which no data were available in our study.

In conclusion, this study provided an overall picture of potential determinants of vitamin D status in the same data set, including detailed data on sun exposure, dietary intake of vitamin D, genetic polymorphisms, and sociodemographic and lifestyle factors collected on a large sample of French middle-aged adults. This approach allowed identifying several factors that independently modulate vitamin D status. Some key determinants pertained to non-modifiable risk factors such as gender, age, and main polymorphisms of the *GC* gene. Although dietary vitamin D intake seemed to have low influence on vitamin D status, several modifiable factors were identified, such as daily-life sun exposure (efficient even at low levels), physical activity, and normal-weight maintenance. These factors should be targeted by public health policies in order to improve vitamin D status of the general population, while avoiding active/intensive sun exposure, in line with recommendations for skin cancer prevention.

MATERIALS AND METHODS

Study population

The SU.VI.MAX study is a population-based, double-blind, placebo-controlled, randomized trial (Trial Registration clinicaltrials.gov NCT00272428) initially designed to assess the effect of a 7.5-year daily antioxidant supplementation on the incidence of cardiovascular disease and cancer (Hercberg *et al.*, 2004). A total of 13,017 participants were enrolled in 1994–1995. All of them provided written informed consent. The study was conducted according to the Declaration of Helsinki guidelines and was approved by the Ethical Committee for Studies with Human Subjects at the Paris-Cochin Hospital (CCPPRB n°706) and the ''Commission Nationale de l'Informatique et des Libertés'' (CNIL n°334641). Participants were advised not to take any spontaneous supplementation during the study period. Health events were self-declared by participants during follow-up. All information was reviewed by an independent expert committee, and cases were validated by pathological report.

A nested case-control study was set up to investigate the association between vitamin D status and cancer risk and thus included all first primary incident cancer cases diagnosed between 1994 and 2007 ($n=928$) and two matched controls per case ($n=1,850$). Controls were randomly selected among the participants of identical sex, age, intervention group, and season of blood draw and without cancer diagnosis by the end of follow-up. The present study focuses on the controls of this nested case-control study. Baseline data collection has been described elsewhere (Hercberg *et al.*, 2004) and is detailed in Supplementary Materials and Methods 1 online.

Plasma 25OHD and PTH concentrations' assessment

Baseline (1994) plasma samples were used to determine the concentrations of 25OHD and PTH. Total plasma 25OHD assay was performed using Roche Cobas electrochemoluminescent immunoassay (Roche Diagnostics, Meylan, France), based on the principle of competitive binding. Eight samples of known 25OHD concentrations were tested in 42 separate assays to assess interassay precision. Eight samples of known concentrations were tested 21 times in the same assay to assess intraassay precision. The intraassay and interassay coefficients of variation were <10%. 25OHD had an intraassay coefficient of variation equal to 4.5% and an interassay coefficient of variation equal to 6.6%.

Plasma PTH concentration was assessed with the Roche Cobas electrochemoluminescent immunometric assay (Roche Diagnostics; Rakel *et al.*, 2005).

Genotyping and quality control

One-to-three SNPs were selected for each gene of interest (*VDR, CYP24A1, GC, RXR,* and *CASR*) on the basis of two criteria: (1) most common polymorphisms in Caucasian populations (http://www.ncbi.nlm.nih.gov/guide/howto/view-gen-freq/) and (2) predicted functional effect according to the PUPA database (http://snpeffect.vib.be and http://pupasuite.bioinfo.cipf.es/). Genomic DNA was extracted from each patient's mononuclear cells in peripheral blood using a MagNA Pure Compact Instrument with a magnetic-bead technology for the isolation process according to the manufacturer's instructions (Roche Diagnostics). Genetic polymorphisms were assessed by allelic discrimination using fluorogenic probes and the 5′ nuclease (TaqMan) assay (Applied Biosystems, Foster City, CA). Quality control of genotyping was carried out for each SNP by investigating any departure from Hardy–Weinberg equilibrium and comparing observed distributions to those of European reference populations: CSHL-HapMap-CEU and 1000GENOMES-phase_1_EUR (http://www.ensembl.org/) by χ^2-tests.

Statistical analyses

Among the 1,850 eligible participants, several were excluded for taking a medication containing vitamin D ($n=12$), antecedent of epilepsy ($n=3$), chronic renal failure ($n=3$), or less than two dietary records provided within the first 2 years of the study ($n=4$). Thus, 1,828 subjects remained for analysis.

The dwelling latitude of the administrative center was retrieved for each department of living (metropolitan France). Participants completed a 14-item questionnaire on lifetime sun exposure and protection behaviors, specifically developed in the context of the SU.VI.MAX study, with six questions investigating awareness of risks related to sun exposure. Following, a validated score of intensity of lifetime sun exposure was computed by principal component analysis for each participant (continuous variable; Guinot *et al.*, 2001; Ezzedine *et al.*, 2008, 2013; Elfakir *et al.*, 2010). In addition, as described in a previous publication (Guinot *et al.*, 2001), three additional scores, related both to sun exposure and physical activity dimensions, were also computed (continuous variables): practice of mountain sports, nautical sports, and outdoor hobbies.

Associations between vitamin D status and the following parameters were assessed: gender, age, BMI (BMI = weight/height^2), physical activity, smoking status, educational level, sex-specific quartiles of dietary intakes of vitamin D and alcohol, latitude, score of intensity of lifetime sun exposure, Fitzpatrick phototype, and month of blood draw. Multivariate models included all these variables and were additionally adjusted for the number of dietary records provided by the subjects. We verified that all tolerance measures were $\geqslant 0.7$, indicating no collinearity problem between covariates (Menard, 2002; O'Brien, 2007). 25OHD plasma concentration was first considered as a continuous variable in multivariate linear regression models. A Box–Cox transformation was applied to the continuous 25OHD variable to improve normality. Then, the probabilities of 25OHD deficiency ($\leqslant 10\,ng\,ml^{-1}$) and insufficiency ($>10$–$\leqslant 20\,ng\,ml^{-1}$) were modeled by unconditional multivariate polytomous logistic regression analysis (Engel, 1988; reference category = 'normal' status, i.e., $>20\,ng\,ml^{-1}$; 25OHD status treated as a nominal variable). These thresholds were based on the US Institute of Medicine's recommendations for the general population (Institute of Medicine, 2011). Odds ratios (ORs) and 95% CIs were computed. Associations between scores of mountain and nautical sports and outdoor hobbies and vitamin D status were investigated in multivariate models that included all previously cited variables.

Associations between each SNP (coded as wild/heterozygous/mutant types) and vitamin D status were assessed separately by linear regression and polytomous logistic regression models adjusted for all previously mentioned nongenetic factors.

As 25OHD and PTH are known to be inversely correlated and may both be associated with the study covariates (Pilz *et al.*, 2012; Touvier *et al.*, 2014), we have also performed the same linear regression models with PTH instead of 25OHD concentration.

All statistical tests were two sided, and $P<0.05$ was considered significant and was not adjusted for multiple testing. All analyses were performed with SAS software (v9.3, Cary, NC).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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DISCLAIMER

The funders had no role in the design, implementation, analysis, or interpretation of the data.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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